that might neutralize the virus, including maternal antibodies, breast-feeding, interfering bacterial or viral agents, and malnutrition. In addition, although both vaccines protected against the full range of serotypes in circulation in the trial population, Rotarix was less efficacious against the G2 strains, and it remains to be seen how the vaccines will perform in settings where nonvaccine serotypes are more prevalent. Both vaccines will need to demonstrate their efficacy in the difficult settings of developing countries if we are to achieve our goal of maximally decreasing global deaths from diarrhea. Fortunately, trials of the Rotarix vaccine have begun in South Africa and will start in Bangladesh and Malawi in the near future. In their report on Rotateq, the investigators indicate the need for Merck to conduct similar trials in the developing world, but no definite plans have been announced.

Anticipating the results of these trials, the Global Alliance for Vaccines and Immunization, the World Health Organization, and the Bill and Melinda Gates Foundation are encouraging and supporting the accelerated introduction of rotavirus vaccines in the poorest countries of the world, where rotavirus remains a fatal disease. Once the efficacy of these vaccines can be established in these populations, mechanisms to finance the introduction of vaccines, ensure a sustainable and affordable supply of vaccines, and expedite the introduction of these vaccines into routine immunization programs should become a global priority. The two reports in the *Journal* document these very large trials, conducted before licensure, to demonstrate both the safety and efficacy of these new vaccines against diarrhea, the second most common disease in children. As vaccines become licensed and used in the United States and Europe, we should expect to see a substantial reduction in winter hospitalizations, visits to doctors and clinics, and parents' workdays lost due to childhood diarrhea. With the successful introduction of rotavirus vaccines in industrialized countries, the global health community will be charged with expediting the availability of these lifesaving vaccines at an affordable price in the developing world. After a long period of waiting, the time for a rotavirus vaccine may have finally arrived.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Intraperitoneal Chemotherapy Comes of Age

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Patients with advanced epithelial ovarian cancer typically receive intravenous taxane and platinum-based chemotherapy in an attempt to eradicate residual disease after surgical debulking. This treatment yields overall median survivals of approximately 37 months in patients with suboptimally debulked disease (residual tumor, >1.0 cm in diameter) and 49 months in those with optimally debulked disease (residual tumor, ≤1.0 cm in diameter).[1] Despite high response rates, in most patients relapse occurs, and efforts to improve treatment by escalating the doses of intravenous chemotherapy have been largely unsuccessful.[2] In contrast to intravenous drug administration,

the intraperitoneal route is capable of achieving high local concentrations of drugs such as cisplatin, with generally acceptable systemic side effects.[3] This strategy is particularly attractive in the treatment of a disease such as ovarian cancer, which remains largely restricted to the abdominal cavity for most of its natural history. The pharmacologic advantage of the intraperitoneal route for drugs such as cisplatin and paclitaxel is considerable, with intraperitoneal-to-plasma concentration ratios in the range of more than 20 and 1000, respectively.[4] This route allows the escalation of the dose of chemotherapy to a level that is not possible to achieve safely with intravenous drug administration.

In this issue of the *Journal*, Armstrong et al.[5] report compelling evidence in support of intraperitoneal chemotherapy for patients with newly diagnosed stage III, optimally debulked epithelial ovarian cancer. Patients in the Gynecologic Oncology Group (GOG) trial who had undergone optimal debulking were randomly assigned to a control group receiving intravenous paclitaxel and intravenous cisplatin or to an experimental group receiving intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8. With a median follow-up of 50 months, there was a statistically significant prolongation of median progression-free survival and overall survival in the intraperitoneal group (a benefit of 5.5 and 15.9 months, respectively) associated with a reduction of 25 percent in the risk of death. A 15.9-month improvement in median overall survival is one of the largest benefits ever observed for a new therapy in gynecologic oncology.

Drugs delivered by the intraperitoneal route penetrate only to a depth of a few millimeters beneath the tumor surface.[6] Thus, patients with relatively small-volume residual disease (i.e., optimally debulked) are expected to benefit most from this approach. However, even small-volume tumor implants may extend well beneath the peritoneal surface, and patients with stage III disease frequently have metastases at other sites, such as retroperitoneal lymph nodes.[7] Eradication of disease in such sanctuaries requires chemotherapy that is delivered through the bloodstream. In this regard, a substantial fraction of cisplatin administered by the intraperitoneal route will eventually be absorbed systemically.[3] It follows that the administration of intraperitoneal cisplatin on day 2 in the GOG trial accomplishes two important goals: the achievement of high drug concentrations within the peritoneal cavity and the systemic delivery of the drug to hidden sites of disease outside the abdomen. In contrast to cisplatin, however, paclitaxel is poorly absorbed into the systemic circulation when administered by the intraperitoneal route. For this reason, the GOG trial was designed to include both intravenous paclitaxel on day 1 and intraperitoneal paclitaxel on day 8, to ensure adequate systemic delivery of the drug while at the same time achieving high drug concentrations within the peritoneal cavity.

The side effects of intraperitoneal chemotherapy included a high incidence of catheter-related complications, abdominal pain, metabolic abnormalities, and neuropathy. Almost half the patients received only three or fewer intraperitoneal courses because of toxic effects, often catheter-related (e.g., infection, blockage, or leak), and only 42 percent of the patients completed six cycles of the planned intraperitoneal therapy. Patients who underwent resection of the left side of the large bowel during the initial debulking surgery were less likely to begin intraperitoneal treatment.[8] Patients removed from the intraperitoneal group were generally able to complete a total of six cycles of first-line chemotherapy by switching to conventional intravenous administration for the remainder of the treatment. It is remarkable that such a clinically meaningful survival advantage was observed, despite the high attrition rate in the intraperitoneal group, suggesting that a substantial benefit from intraperitoneal chemotherapy may occur within the first several cycles of treatment. Although this hypothesis is provocative, the relationship between the number of intraperitoneal cycles received and the magnitude of the benefit can be assessed only in a randomized trial.

Many efforts to improve the tolerability of intraperitoneal therapy could be considered, including reduction of the dose of intraperitoneal cisplatin on day 2, administration of intravenous paclitaxel on day 1 over 3 hours instead of 24 hours, or omission of intraperitoneal paclitaxel on day 8 until tolerance of the first cycle of intraperitoneal cisplatin can be assessed. Although these measures are reasonable, it is unknown whether they will reduce the toxic effects and still preserve the benefits of the intraperitoneal

approach. The intraperitoneal placement of a single-lumen venous-access device attached to a subcutaneous port may also be preferable, as this device appears to have a lower tendency to fibrous-sheath formation or the development of a bowel obstruction, as compared with fenestrated catheters.[9] Although there is also interest in the use of intraperitoneal carboplatin instead of intraperitoneal cisplatin, in the hope of reducing toxic effects while preserving efficacy.[10] Although there is a pharmacologic advantage to intraperitoneal carboplatin, it is not known whether carboplatin is as effective as cisplatin when administered by the intraperitoneal route. This important question can be addressed only in a randomized trial.

The results of the GOG trial, taken together with data from two other randomized trials,[11,12] will influence clinical practice. It will now be appropriate for physicians to discuss intraperitoneal therapy with selected patients who have newly diagnosed, optimally debulked disease, making certain that these patients have a clear understanding of the benefits as well as the greater risk of side effects. Unlike the introduction of a new drug into patient care, however, the use of intraperitoneal therapy requires a new set of logistics for clinical practice. These include the need to schedule catheter placement (unless this was performed during the initial surgery) and multiple treatment visits as well as the need to provide intensive physician and nursing support for managing infusion-related abdominal pain and infections at the catheter site. With the assistance of a skilled oncology nursing staff, it should eventually be possible for many oncologists to administer the GOG regimen, or a modification of it, effectively. However, as is the case with any specialized technique, in the short term physicians unfamiliar with intraperitoneal therapy might consider referring appropriate patients to centers with expertise in this procedure.

As anticipated on the basis of the toxicity profile, the intraperitoneal regimen used in the GOG trial is associated with a reduced quality of life during the therapy and shortly after its completion, but there was a return to baseline one year after completion.[5] Given the survival advantage of the treatment, many patients will be willing to undergo intraperitoneal therapy, even after being informed of its short-term effects on the quality of life, and others will not be willing to do so. For these reasons, the decision to use intraperitoneal chemotherapy should be individualized. Despite increased toxic effects and the more complicated logistics of drug administration, the data from the GOG trial establish intraperitoneal chemotherapy as an important advance in the first-line treatment of patients with optimally debulked stage III disease.

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